

# A rare case of grave's disease after SARS-CoV-2 vaccine: is it an adjuvant effect?

A. TAIEB<sup>1,2</sup>, N. SAWSEN<sup>1,2</sup>, B.A. ASMA<sup>1,2</sup>, S. GHADA<sup>1,2</sup>, E. HAMZA<sup>1,2</sup>,  
H. YOSRA<sup>1,2</sup>, M. AMEL<sup>1,2</sup>, C. MOLKA<sup>1,2</sup>, K. MAHA<sup>1,2</sup>, A. KOUSSAY<sup>1,2</sup>

<sup>1</sup>Department of Endocrinology, University Hospital of Farhat Hached Sousse, Sousse, Tunisia

<sup>2</sup>University of Sousse, Faculty of Medicine of Sousse, Sousse, Tunisia

**Abstract.** – The COVID-19 virus has been responsible for the development of several systemic diseases. Recently, the COVID-19 vaccine has also been incriminated in the development of autoimmune diseases. Currently, researchers have focused on the relationship between the COVID-19 vaccine and the activation of autoimmune phenomenon. We report a case of Graves' disease (GD) whose symptoms appeared 3 days after vaccination against COVID-19.

A forty-three-year-old female, without pathological history, presented with diarrhea and palpitation. She received her first SARS-CoV-2 Vaccine dose (Pfizer-BioNTech), in August 2021. Three days after the vaccine, she felt palpitations, sleep disorders, muscle weakness, and heat intolerance. On examination, her pulse was 119 beats per minute, she weighed 63 kg, and she had lost 4 kg in only two months. GD was suspected. Thyroid hormone testing showed low thyroid-stimulating hormone, and an elevated serum free thyroxine hormone T4 level. Serology tests were positive for TSH receptor autoantibodies (TRAB). A GD induced by adjuvants of SARS-CoV-2 vaccine has been retained as a final diagnosis. Several autoimmune diseases have been attributed to adjuvant-induced autoimmune/inflammatory syndrome, including systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis, and recently few cases of GD have been explained by this phenomenon.

*Key Words:*

Graves' disease, COVID-19, Thyroid, Endocrinopathy, Adjuvants, Vaccines, ASIA syndrome.

## Abbreviations

COVID-19: Coronavirus disease 2019; AID: Auto-immune disease; GD: Graves' disease; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TSH: thyroid-stimulating hormone; T4: thyroxine hormone; TRAB: TSH receptor autoantibodies; ASIA: Autoimmune Syndrome Induced by Adjuvants.

## Introduction

Coronavirus disease 2019 (COVID-19) has affected millions of people around the world. The elderly, people with certain coexisting diseases and frontline staff are most at risk for COVID-19 and its complications. This new virus can cause many systemic disorders, including auto-immune diseases (AID)<sup>1</sup>. Autoimmune dysthyroidism has recently been linked to COVID-19 infection with a probable direct effect on the gland<sup>2</sup>.

Lately, the emergent use of COVID-19 vaccine has demonstrated its effectiveness in protecting against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

In general, the adverse effects of the vaccine are well tolerated, but immune-related reactions have been reported in some predisposed patients<sup>1</sup>. It is due to the activation of autoimmune phenomena that disturb the immunological balance of the host<sup>3</sup>. This is attributed to the autoimmune syndrome induced by adjuvant (ASIA), a substance used to enhance the immune response of vaccines<sup>4</sup>. However, cases of GD induced by adjuvants of SARS-CoV-2 vaccine are exceptional in the literature and has been reported only in few cases<sup>5,6</sup>. We herein report a rare case of a patient who developed GD 3 days after COVID-19 vaccine.

## Case Presentation

We report the case of a forty-three-year-old female, a mother of three children, without any pathological history. She did not have any personal or family history of autoimmune or endocrine diseases, nor a history of upper respiratory system infection or COVID-19. She presented with diarrhea and palpitations. She received her first SARS-CoV-2 Vaccine dose (Pfizer-BioNTech), composed of a nucleoside RNA encoding a

**Table I.** Hormonal and antibodies assessments.

	Result	Reference range
TSH (mIU/ml) before vaccination	1.4	0.38-5.33
TSH (mIU/ml) after vaccination	< 0.002	0.38-5.33
TSH (mIU/ml) after after a 3-months follow-up	1.22	0.38-5.33
T4 (pmol/l)	65.96	12-22
TRAB (IU/l)	3.1	< 1

TSH (thyroid-stimulating hormone), T4 (free thyroxine hormone), TRAB (TSH receptor autoantibodies).

modified SARS-CoV-2 spike protein, on August 18, 2021. Three days after the vaccine, she felt palpitations, sleep disorders, muscle weakness, and heat intolerance. On examination, her blood pressure was 120/80 mmHg, her heart rate was 119 beats per minute, and her respiratory rate 17 breaths per minute. She weighed 63 kg, after she had lost 4 kg in only two months. Her height was 160 cm, and her body-mass index was 24 kg/m<sup>2</sup>. She had hand tremors. The thyroid was palpable but there were no goiter or compressive signs, nor were there any cervical lymphadenopathy. In view of this clinical presentation, Graves' disease (GD) was suspected.

Thyroid hormone testing showed low TSH, and an elevated serum Free T4 level. Serology tests were positive for TRAB (Table I).

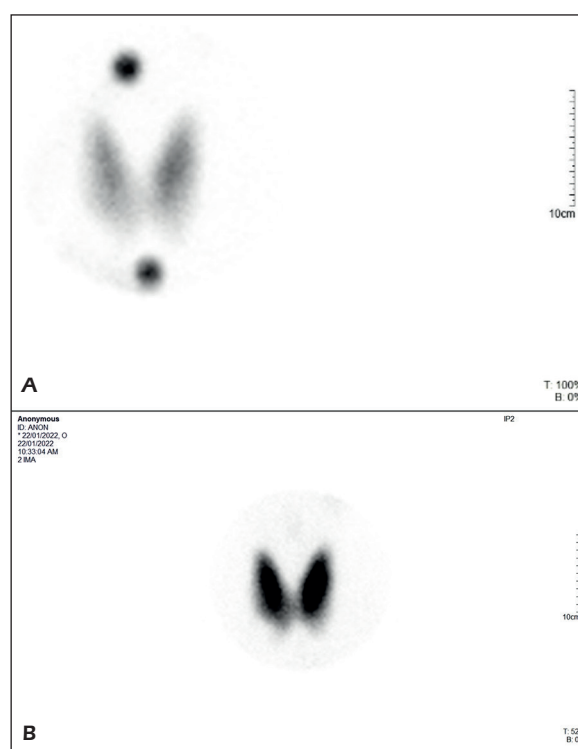
Thyroid scintigraphy with Technetium-99m showed a normal size of the gland, with uniform increased uptake of isotope (Figure 1A-B).

She was diagnosed with GD. On standard biological tests, she had normal liver function and a normal blood count (Table II). She was treated with Thiamazol 30 mg and Propranolol 20 mg per day. After a follow-up of 3 months, we noticed a good tolerance of the treatment, with a return to clinical and biological euthyroidism (Table I).

## Discussion

COVID-19 pandemic was at the origin of the revelation of several autoimmune endocrine diseases. Since then, several research works have tried to demystify this phenomenon<sup>5,6</sup>.

Recently, few cases of AID have been reported such as primary adrenal insufficiency following COVID-19 infection<sup>7</sup>. Also, cases of Guillain-Barré syndrome<sup>8</sup> and autoimmune haemolytic anaemia, autoimmune thrombocytopenic purpura have been reported as a related disease to COVID-19 infection<sup>2</sup>.



**Figure 1. A,-B,** Technetium-99m thyroid scan showing normal fixation.

SARS-CoV-2 infection is responsible for a state of hyperinflammation that may trigger an immunological hyperactivation that may explain the onset of AID<sup>6</sup>.

**Table II.** Hematological and hepatic biological tests.

	Result	Reference range
WBC (mm <sup>3</sup> )	6150	4000-10000
Hb (g/dl)	11.3	12.5-15.5
ASAT (IU/l)	38	< 40
ALAT (IU/l)	37	< 40

WBC: White blood cells), Hb: Hemoglobin, ASAT: Aspartate-Amino-Transferase, ALAT: Alanine-Amino-Transferase.

Some studies<sup>5,6</sup> have published cases of patients with thyroid diseases in relation to COVID-19, such as, Hashimoto thyroiditis, subacute thyroiditis and GD.

GD is the most common etiology of hyperthyroidism. Its annual incidence is of 20 to 50 cases per 100,000 persons<sup>9</sup>. GD mainly concerns patients aged between 30 and 50 years<sup>10</sup>.

To confront the COVID-19 pandemic, several vaccination campaigns were rapidly deployed around the world. This resulted in a high level of protection against the virus.

To provide more protection, several vaccination techniques have been developed using various adjuvants<sup>4</sup>. Adjuvants are substances used to enhance the post-vaccine immune response. They are capable of altering the host immune system, via polyclonal activation of B cells and effects on cellular immunity<sup>4</sup>. Aluminium is one of the most frequently used adjuvant in vaccines<sup>11</sup>.

In 2011, the ASIA syndrome, was presented by Shoenfeld and Agmon-Levin, as an entity that explains the different mechanisms leading to an autoimmune response, when exposed to a vaccine adjuvant<sup>4</sup>. The main symptoms of ASIA syndrome are fatigue, which is the most disabling, arthralgia, neurological signs and eventually cognitive alterations and sleep disorders<sup>12</sup>. A survey conducted in 2016 on 300 patients revealed that ASIA syndrome was more frequent in women than in men, with an average age of 38 years<sup>11</sup>.

A recently published study<sup>11</sup> of 500 cases of adjuvant-induced autoimmune disease showed that the average time from exposure to vaccination to onset of symptoms was one week (2 days-5 years). Several AID have been described as adjuvant-induced, including systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis, primary ovarian failure<sup>4</sup>.

Few cases of GD have been reported as following COVID-19 vaccination. To the best of our knowledge, this is the seventh case report<sup>13</sup>.

In the published cases of GD after vaccination with COVID-19, the age of onset of the disease ranged from 28 to 70 years, with a female predominance. The patients received different types of vaccines (BNT162b, CoronaVac, ChAdO)<sup>13</sup>. The onset of symptoms varied from 2 days to one month<sup>13</sup>.

Several other complications of GD have been reported after COVID-19 vaccination, including worsening of symptoms of thyrotoxicosis and activation of eye disease in a patient with a history of GD<sup>1</sup>.

Despite the extensive vaccination against SARS-CoV-2 globally, very rare cases of induced dysthyroidism<sup>13</sup> have been reported. This could either be related to underreporting or compatible with the rare incidence of post-vaccination adverse events in general. A systematic study of SARS-CoV-2 vaccine recipients regarding their changes in thyroid function and autoantibodies may shed light onto the extent of this problem.

## Conclusions

Our case showed that COVID-19 vaccine is incriminated in the revelation of autoimmune endocrine disease which could be explained by ASIA syndrome. The development of GD may occur within few days after the vaccination.

As a result of the COVID-19 vaccination program, the number of severe SARS-CoV-2 infections has decreased significantly. Of course, all vaccinations carry risks. But in this pandemic situation, the benefits of the vaccine outweigh the risks. In addition, autoimmune endocrinopathies are seen in vulnerable individuals. These patients require consent prior to vaccination and subsequent follow-up for early detection of any AID.

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### Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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### Informed Consent

An oral and informed consents were obtained from the patient.

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### Patient Consent

A written informed consent was obtained from the patient before the beginning of the writing. The Local Ethical Committee approved the publication.

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### ORCID ID

Ach Taieb: 0000-0002-8387-8278.

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